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HYDROPHOBIA.

REPORT

OF THE SECTION ON

Anatomy, Physiology and Pathology.

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Report of the Section on Anatomy, Physiology, and Pathology.

HYDROPHOBIA.

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Of the many subjects suitable for the Report of the Chairman of this Section I have selected *hydrophobia*, on account of the numerous and important contributions to its pathology and etiology during the past four years, and especially because the time has come when we can form an intelligent estimate of the value of the Pasteurian inoculations against hydrophobia. Although these inoculations constitute the central point about which controversy has waged, it is not to be forgotten that Pasteur's discoveries and the investigations aroused by them have shed much light in many directions upon the nature of one of the most mysterious and fatal diseases. Whatever had been the outcome of Pasteur's antirabic treatment, his researches upon hydrophobia would still have remained an important scientific contribution to our knowledge of the disease.

We are still insufficiently informed concerning the pathological anatomy of hydrophobia. I have had opportunity to make post-mortem examination of three cases of hydrophobia in human beings. In one case serial microscopical sections were made of the medulla oblongata and pons from the second cervical nerve upward. The lesions consisted in small hemorrhages, in accumulations of small round cells in large numbers, both in the peri-vascular lymph spaces, and in scattered foci in the neuroglia between the nerve elements, and in thrombi, composed of hyaline material and of leucocytes, in small blood vessels. These lesions were microscopical, and



their extent and distribution could be determined only by the examination of a large number of sections from different parts. The lesions were especially well marked in and near the nuclei of origin of the spinal accessory, pneumogastric and glosso-pharyngeal nerves, and in the motor nucleus of the trigeminus. Cases have been reported in which even more extensive lesions than these have been found; their intensity depending apparently in large measure upon the duration of the disease. While it can not be claimed that these lesions are peculiar to hydrophobia, or by themselves suffice for its diagnosis, it is incorrect to suppose that hydrophobia is a disease without demonstrable anatomical lesions which bear a manifest relation to the symptoms of the affection.

Far more important than the additions to our knowledge of the pathological anatomy of rabies following Pasteur's discoveries, are the contributions to a better comprehension of the causation of the disease. Before Pasteur's publications on hydrophobia, dating from 1881, about all that we knew of the virus of rabies was that it is contained in the salivary glands and their secretions, and that infection often follows the bites of rabid animals. We knew that after characteristic symptoms appeared, the disease was uniformly fatal; but we possessed no positive means of diagnosis. Hence it was impossible to secure trustworthy statistics of the mortality among those bitten by rabid animals; for we could not determine accurately how many of the animals were rabid. There obtained among a few an unwarrantable scepticism even as to the existence of such a disease as hydrophobia.

We now possess positive means of diagnosis of hydrophobia by the inoculation of animals, particularly of rabbits; so that the last vestige of doubt as to the existence of the disease must disappear. We have now valuable information concerning the properties of the rabid virus, its distribution in the infected body, the manner of its transmission, the singular differences in its action, according to the mode and seat of its inoculation, and the means of producing immunity against its destructive action on the body.

Although there is no reason to doubt that the infectious agent of rabies is a micro-organism, no actual demonstration of this organism has yet been made. If fluids containing the

rabid virus be filtered through substances impenetrable to particulate matter, the filtrate is free from infectious properties. In the Pathological Laboratory of the Johns Hopkins University, we have had opportunity to study the effects of the rabid virus upon a series of rabbits, the original material having been obtained from the medulla oblongata of a man dead of hydrophobia. We were able abundantly to confirm the statements of Pasteur and others as to the behavior of these animals when inoculated in succession with the virus of rabies. We endeavored by cultures and by staining re-agents to demonstrate some specific micro-organism; but with entirely negative result. A repetition of the methods indicated by Fol, failed to confirm his statements as to the presence in the nervous centres of a demonstrable species of bacteria. But while we are not acquainted with the specific organism causing hydrophobia, we know many of its properties.

The virus of rabies is destroyed by comparatively low temperatures, exposure for one hour to a temperature of 50° C. (122° F.) sufficing for this purpose. It is killed in a short time by drying, certainly within four days when exposed in thin layers capable of rapid desiccation. It is said to be destroyed by exposure to the direct rays of the sun, even when under conditions preventing elevation of temperature. According to Babes, the virus is more resistant to the action of corrosive sublimate and carbolic acid than most bacteria; but it loses its infectious properties after exposure for three hours to the action of 0.1 per cent. sublimate, or of 1 per cent. carbolic acid solution. Galtier has pointed out a fact of practical importance, that the virus of rabies may be demonstrated after forty-four days, and perhaps longer, in the cadavers of buried animals. An easy means of preserving the virus is to place the brain or cord of the infected animal in pure glycerine, which may be diluted with water, and which should be occasionally changed. In cases in which persons are bitten by animals suspected of rabies, the animal should be secured and watched, and if it dies, the nervous centres should be removed and preserved in dilute glycerine for subsequent inoculation of rabbits, whenever such inoculation can not be performed at once by a competent person.

It has been ascertained that the certainty of infection with rabies depends largely upon the part of the body and the character of the tissues into which the virus is inoculated. The disease develops always and with the shortest period of incubation after inoculation of the virus into the brain, or upon its surface. Those who have asserted that the same group of symptoms may follow the intra-cranial inoculation of substances other than rabid virus, have fallen into serious error. Equally certain in the effects are inoculations of the virus into the eye, although here the period of incubation is less definite. Inoculations into the substance of nerve trunks appears to be uniformly successful in rabbits, but somewhat less certain in dogs, although even in the latter animal inoculation into the pneumogastric nerve does not fail. Intra-venous injection does not produce the disease in ruminants unless large quantities of the virus are used; but it is a ready means of conferring immunity upon these animals. The same mode of injection succeeds often in dogs, and usually in rabbits, in producing the disease; but it may fail in both classes of animals. Especial importance attaches to the behavior of subcutaneous injections of the virus of rabies. Dogs often resist infection from the injection of considerable quantities of the most intense virus into the subcutaneous tissue. Indeed, Pasteur finds that the more intense the virus, and the larger the quantity injected subcutaneously, the less likely is the dog to develop rabies, and the more certain is it to acquire immunity. Ferran's super-intensive method of producing immunity in human beings, is to inject at once the strong virus into the subcutaneous tissue. Although he has done this in over 400 cases without injury, the method does not rest upon a safe basis so far as experiments upon dogs are concerned; for these animals sometimes contract the disease after this mode of inoculation. Infection is more likely to follow injections into the muscular tissue than into the subcutaneous connective tissue. Of course the injection of the virus into the subcutaneous tissue by means of a hypodermic syringe can not be considered analogous to inoculation by means of bites which wound the skin and subcutaneous tissues. Di Vestea and Zagari have shown that while simple subcutaneous injections are often unsuccessful in producing rabies, the application of the virus to the divided

ends of nerve filaments in a cutaneous wound is generally efficacious in causing the disease. Although deep and severe bites of rabid animals are the most dangerous, hydrophobia may result simply from a mad dog licking an abrasion or scratch. Intra-peritoneal injections of the rabid virus produce the disease in rabbits and guinea-pigs, if considerable quantity of the virus be used.

As regards the distribution in the body of the infectious material of rabies, it has been demonstrated by Pasteur that in human beings or animals which have died of hydrophobia, the virus is contained most abundantly in the central nervous system, and especially in the medulla oblongata and brain. It is found also in the nerves near their exit from the brain and cord, but less constantly and in less amount in the peripheral nerves. The virus is probably always present in the salivary and lachrymal glands, and sometimes in the pancreas, but it is usually absent from the blood, kidneys, spleen and liver. Only exceptionally is it present in the mammary glands and the milk. It is very rarely transmitted to the foetus through the placenta. We see, therefore, that the virus is very unequally distributed in the body, and that its chief habitat is the central nervous system.

A point of much interest is the manner in which the virus is conveyed from the seat of inoculation to the central nervous system. The chief possibilities which present themselves are transmission by the blood-current, by the lymph-current and along the nerve trunks. There is evidence that the virus may be conveyed in each of these three ways. The production of the disease by intra-venous and by intra-peritoneal injections of the virus, speaks for the first two modes of transmission. But there are considerations which favor the view that the usual mode of transmission is along the nerves. Inoculations made directly into nerve trunks are more certain to produce rabies than either intra-venous or intra-peritoneal injections, and by the first method a smaller quantity of the virus suffices. The symptoms of rabies, which are chiefly nervous, frequently bear a certain relation to the seat of inoculation in the order of their development. Thus when the inoculation is made into the anterior extremities or the head, the first symptoms are bulbar, whereas, when the inoculation is into the posterior ex-

trremities or tail, spinal symptoms, especially paralysis of the posterior extremities, appear first. No such regularity in the sequence of symptoms is observed after intra-venous injections. In a large proportion of cases of hydrophobia in human beings, the first symptoms are referable to disturbances in the nerves in or near the injured part, and paraplegia or the paralytic form of rabies is most likely to follow bites in the lower extremities. By killing animals at the proper period, it has been ascertained that after inoculation in the head or anterior part of the body the virus makes its appearance in the medulla oblongata sooner than in the posterior part of the spinal cord, while the reverse holds true when the inoculation is made in the tail or the posterior extremities. The virus propagates itself in steps, as it were, along the spinal cord. Roux and Bardach have found the virus present in the nerves of a bitten extremity when it has been absent in the corresponding nerves of the opposite side; whereas, the reverse of this has never been observed. Di Vestea and Zagari have succeeded, in rabbits, by making resections of the spinal cord, and keeping the divided ends separated by a plug of antiseptic cotton in preventing the virus from extending from one segment of the cord to the other, so that, after intra-cranial inoculations, the upper segment contained the virus and the lower did not, and after inoculations into the sciatic nerve, the virus was prevented from passing from the lower to the upper segment. Division of a nerve trunk above the point of inoculation may retard, but does not prevent the development of the disease, but here there is the possibility of the propagation of the virus along anastomotic nerve filaments. It must be admitted that the facts and experiments which have been mentioned speak strongly for the view that the virus passes along the nerves, although we have no information as to how this is accomplished, and it is not worth while to consider the theories which have been framed to explain this interesting and curious phenomenon.

One of the most important discoveries of Pasteur in this subject, is that the virus of rabies may undergo changes in certain of its properties by transmission through a series of animals of the same species. The principal change is an increase of virulence, characterized by a shortened period of incubation of

the disease. This change is brought about by the transmission of the virus through a long series of rabbits, each one being inoculated beneath the dura mater with an emulsion made with the medulla oblongata of the preceding rabbit which has died of hydrophobia. When a rabbit is inoculated beneath the dura with the medulla of a dog dead of rabies, the so-called rabies of the street (*rage des rues*), the period of incubation of the disease is usually between 15 and 20 days, and apparently never less than 11 days. By inoculating intra-cranially rabbits in series, beginning with this first rabbit, the period of incubation is gradually reduced to seven and finally to six days, at which it remains indefinitely. In the series of rabbits employed by Pasteur for his preventive inoculations, the period of seven days had been reached before the 80th passage, and at the time of the 178th passage, the period of incubation had been for a year 6 days in at least two out of three of the rabbits. The virus from the medulla of rabbits with this uniformly short period of incubation of 6 or 7 days is spoken of as fixed virus (*virus fixe*). The time required for obtaining the fixed virus may be very much shortened by employing young rabbits and by inoculating several at a time, selecting for successive inoculations from each group the one presenting the shortest period of incubation. In this way Hogenes obtained the fixed virus in the 16th passage, about five months after the beginning of the successive inoculations.

If the medulla of a rabbit which has died of inoculation with the fixed virus be preserved in a dry atmosphere, its virulence progressively diminishes, as is indicated by the lengthening of the period of incubation. The loss of virulence is rapid in proportion to the temperature at which the medulla is kept. The infectious properties, as a rule, disappear at the end of a fortnight if the temperature be from 23° to 25° C. (71.6° — 77° F.), and sooner than this if the medulla be of small size.

The question arises whether these changes in virulence depend upon alterations in the quantity or in the quality of the infectious agent. We judge of the degree of virulence mainly by the length of the period of incubation after the intra-cranial inoculation of a rabbit. It has been shown experimentally that this period may be progressively lengthened by dilution of the virus inoculated, and this fact may be put in evidence in favor

of a quantitative change to explain varying degrees of virulence. On the other hand, fixed virus would seem to differ qualitatively from the virus of rabies of the streets, for no matter how prolonged the period of inoculation may be rendered by dilution of the fixed virus, or in other words, by diminution in the quantity of the infectious agent, if this rabbit develops rabies, its medulla always contains the fixed virus—that is, when inoculated intra-cranially into another rabbit, its period of incubation is 6 or 7 days, which is shorter than ever occurs with the virus from the rabies of the street. Pasteur is inclined to attribute the progressive loss in virulence of the rabbit's medulla preserved in a dry atmosphere, to a gradual diminution in the quantity of the infectious material, rather than to any change in its quality.

It is a significant fact, which should be remembered in judging the results of Pasteur's treatment, that there is a period of so-called latent development of the virus in the central nervous system. In rabbits inoculated with the fixed virus, the period of incubation is six or seven days, but as early as the fourth day the virus has been found in the medulla oblongata. Doubtless, therefore, in human beings the virus is present in the central nervous system for a period before any characteristic symptoms of rabies appear, so that it may readily happen that treatment is begun too late, even when undertaken before there are manifestations of the disease. Careful observation has shown that in rabbits this period is not, strictly speaking, a latent one, but it is accompanied by elevation of temperature, increased frequency of respiration, slowing of the pulse rate and loss of weight, symptoms which point to an action of the rabid virus primarily upon the heat centres and upon the vagus.

It is customary to divide rabies according to its clinical manifestations into two forms, furious or convulsive rabies and dumb or paralytic rabies. A third form, however, should also be distinguished—namely, mixed rabies, which represents a combination of convulsive and of paralytic rabies. The most common form of rabies in human beings is furious or convulsive rabies, but paralytic rabies also occurs in man, especially after bites on the lower extremities, and is more common, according to recent reports, than was formerly believed. In

dogs, furious rabies is the predominant variety, whereas, in rabbits, paralytic rabies is the more common, and in Pasteur's series it became the sole form after inoculation with the fixed virus. A careful study of the symptoms, however, renders less sharp the distinction between furious and paralytic rabies, for in either form it is often possible to distinguish a stage of excitation and a stage of paralysis, but in the furious form the stage of paralysis is short and may be wanting; whereas, in the paralytic form, the stage of excitement is of short duration, and may be characterized only by acceleration of the breathing, elevation of temperature and symptoms referable to irritation of the vagus nerve. There is probably no difference in the quality of the virus causing the two clinical forms of hydrophobia, the distinction depending rather upon the nature of the animal infected, and the seat of inoculation, possibly also upon the quantity of virus inoculated. The only observation in favor of differences in the character of the virus causing the two varieties of rabies are those of Helmann, who claims to have a virus which will produce in rabbits invariably furious rabies, and another virus which produces the customary paralytic rabies, but these observations have not been confirmed, are not free from objections, and are not in harmony with the observations of Pasteur and others, who find that the virus of rabies of the street, which is generally furious in character, produces paralytic rabies in the rabbit, and that the latter causes furious rabies in the dog, there being occasional exceptions to these rules. The occasional occurrence of paralytic rabies in human beings who have not been subjected to treatment after the bite of a mad dog, disproves the assertion of Peter that paralytic rabies is only rabies of the laboratory, and when it has occurred in persons treated by Pasteur's method, it can be attributed only to the anti-rabic inoculations and not to the bite of the animal, an assertion which, moreover, can be positively disproven by experiment, as will be explained subsequently.

There can be no doubt whatever that it is possible to render animals immune against rabies both before and after inoculations which would otherwise cause the disease. The independent and careful experiments of Ernst in this country are free from all partisan bias, and have fully confirmed the statements

of Pasteur and others upon this point. The methods employed by Pasteur for protective inoculation against hydrophobia have been so often and so fully described in medical and other journals, that it is not necessary to repeat the description on this occasion. The method is based upon the injection subcutaneously (sometimes in certain animals into the blood) first of attenuated virus contained in the medullæ, dried for a certain period, of rabbits dead after inoculation with the fixed virus, and then of stronger and stronger virus contained in medullæ dried for shorter periods, until strong or the strongest virus is reached. These inoculations are most effective in preventing the disease when undertaken soon after the reception of the poison, and with a large quantity of virus and with the speedy employment of material containing the strongest virus (*virus fixe*). Animals may be rendered immune by a single injection into the blood or into the subcutaneous tissue of a large quantity of strong virus, whereas dogs which are bitten by mad dogs and which do not develop the disease, as may happen, are not usually left immune, evidently because not sufficient quantity of the virus has been received. Dogs which have once been rendered immune against rabies preserve this immunity for at least two years, and doubtless for a longer period.

The experiments of von Frisch are often quoted in opposition to the validity of Pasteur's conclusions. Von Frisch claimed that it is impossible to produce immunity after the virus of rabies has been received in a manner certain to produce the disease. He urged that Pasteur's experiments demonstrated the possibility of producing immunity only before and not after the reception of the rabid virus. In this latter assertion he was in error. Von Frisch's failure to produce immunity after the reception of the strong virus was due partly to his selection of rabbits for his experiments, and partly to imperfect methods of preventive inoculation. On account of their extreme susceptibility to the rabid virus, and of the short period of incubation after intra-cranial inoculations, rabbits are much less suitable animals for these experiments regarding immunity than dogs. But even in rabbits immunity may sometimes be produced if the preventive inoculations be undertaken speedily after the reception of the virus, and be ac-

cording to the intensive method. Pasteur and others have shown that in a large proportion of cases the development of rabies may be prevented in dogs even after subdural injection of the strongest virus, if preventive inoculations by the intensive method be begun not later than the second day after the reception of the poison. Bardach succeeded in this way in saving 60 per cent. of the dogs inoculated beneath the dura mater. This test is evidently the most severe one to which Pasteur's preventive treatment can be subjected, one far more severe than is required to meet the ordinary channels of infection with rabies in human beings, in whom the period of incubation is longer and the virus is received in less intense form and in situations from which infection is slower and less certain. It must be admitted, therefore, that Pasteur's treatment rests upon a satisfactory experimental basis, and one which forms a complete justification of the application of the treatment to human beings bitten by rabid animals.

We have no positive knowledge as to the manner in which immunity is caused by the Pasteurian vaccination against rabies, any more than we have as to the causation of immunity in other diseases. Pasteur is inclined to attribute the immunity to the action of some substance, which he calls "*matière vaccinale*," contained in the inoculated material, but not identical with the micro-organism causing rabies. That immunity against infectious diseases may be secured by the injection of chemical substances produced by the growth of specific bacteria, was demonstrated first by Salmon and Smith in the case of hog cholera, and has been since demonstrated by Roux and Chamberland for malignant œdema, and by Wooldridge for anthrax. It has not yet been found possible to prove the correctness of Pasteur's supposition in the case of rabies, and although there are arguments in its favor, it is hardly worth while for us to consider further a question at present in so hypothetical a state.

Encouraged by the results of his experiments upon animals, Pasteur, in July 1885, first applied to a human being his method of preventing hydrophobia by successive injections of the virus contained in the rabbit's medulla subjected to drying for different periods, the medulla being taken from rabbits which had died after inoculation with the fixed virus.

During the years 1886, 1887, and the first half of 1888, there have been treated under Pasteur's supervision, either by the simple or by the intensive method of vaccination, 5,374 persons who have been bitten by animals either proven or suspected to be rabid. The mortality from hydrophobia, including even the cases which developed within a day after the cessation of treatment, was for 1886 1.34 per cent.; for 1887, 1.12 per cent.; for the first half of 1888, 0.77 per cent. If the fatal cases which developed within a fortnight after the end of treatment, and in which there is reason to believe that the inception of treatment was too late, be excluded, the mortality for 1886 falls to 0.93 per cent.; for 1887, to 0.67 per cent.; and for the first half of 1888, to 0.55 per cent. From May 1, 1888, to May 1, 1889,* there were treated at the Pasteur Institute, in Paris, 1,673 persons bitten by dogs, either rabid or suspected to be rabid. Of these 6 died during treatment, 4 in less than a fortnight after treatment, and 3 died later than a fortnight following the cessation of treatment. Only the last 3 cases, therefore, are to be counted as failures. If all the deaths, both during and after treatment, be included, which would be illogical, the mortality equals 0.78 per cent.; if only the deaths after treatment be reckoned, the mortality becomes 0.42 per cent.; and if only those occurring more than a fortnight after the end of treatment be estimated, the death-rate sinks to 0.18 per cent. This mortality may be somewhat increased by subsequent deaths, as sufficient time has not elapsed for full completion of the returns. Pasteur, in a recent letter to Sir H. Roscoe, says that up to the end of June, 1889, over 7,000 persons have been treated in his laboratory, and that the general mortality applicable to the whole number of the operations was 1 per cent.

Doubtless a considerable number of cases are included in the foregoing statistics of persons subjected to treatment who have not been bitten by animals actually rabid. How large is this number, it is impossible to say; but even if ample allowance be made for this class of cases, the results of the treatment can hardly be interpreted otherwise than in favor of its efficacy.

It is possible, however, to select from the reports only those cases in which the animal inflicting the injury has been actually

*I have endeavored to bring the statistics of this paper up to the date of its publication (July, 1889), and have therefore added certain statistics which have appeared since the time the paper was read in April, 1889.

proven to be rabid. This proof is the most exact which can be furnished, and consists in the results of the inoculation of animals with the brain or cord of the animal, or in the development of hydrophobia in persons or animals bitten at the same time as those treated. Pasteur's statistics, which are published monthly, are arranged in tables which embrace: *A*—Persons bitten by animals proven to be rabid: *B*—Cases in which the existence of rabies in the animal is certified by a veterinarian: *C*—Cases in which there is reason to suspect rabies in the animal, although the evidence furnished in the foregoing classes was not obtained.

If the cases be analyzed according to this classification, we obtain the following results: Since the beginning of his operations in July, 1885, up to the end of the first half of 1889, there have been treated under Pasteur's supervision 6,950 patients. There were bitten by animals suspected, but not proven to be mad, 1,187, of whom 12, or 1.01 per cent., died; by animals pronounced rabid by veterinarians, 4,686 persons, of whom 44, or 0.94 per cent., died; and by animals proven experimentally to be rabid, 1,077 persons, of whom 15, or 1.39 per cent., died. The similarity of the results in the three classes shows that the second and third groups must contain a large number of cases in which the wounds were inflicted by rabid animals. If we exclude from the preceding statistics those who began treatment a fortnight or more after being bitten, we find the death-rate in Class *C* to be 5, or 0.42 per cent.; in Class *B*, 31, or 0.66 per cent., and in Class *A*, 11, or 1.2 per cent.

The most convincing presentation of the case is to select the results of treatment in persons bitten on the head and face by animals proven to be rabid. In all statistics purporting to give the mortality from the bites of rabid animals, by far the largest death-rate is afforded by the bites on the head and face. I have collected from Pasteur's reports for 1887 and 1888, those bitten on the head and face by animals proven experimentally to be rabid. There were 72 cases, with 4 deaths from rabies during treatment, and 3 following treatment. Of the latter, one was seized three days after the end of treatment, and it is therefore reasonable to suppose that in this case the treatment was begun too late. If this case and

those dying during treatment be excluded, there remain 67 cases bitten on the head or face by animals proven to be rabid, with 2 deaths, a mortality of 3 per cent. I was not able to obtain the data for an analysis of all of the cases in this group since the beginning of Pasteur's treatment; but after collecting these cases, I have met the statement that the total number of persons bitten on the face and neck by animals proven to be rabid is 540; of whom 21 died, leaving a mortality of 3.89 per cent.; but how many of these are fairly attributable to failure of the treatment does not appear. These cases undoubtedly belong to both Class *A* and Class *B*.

Unless it can be shown that the mortality following the bites of rabid animals is as small as that derived from the foregoing statistics, no other conclusion can be drawn than that Pasteur's treatment is efficacious; for we can dismiss as unworthy of consideration all attempts to cast doubt upon the truthfulness of the statistics published by Pasteur. Notwithstanding the outcry of those who assert that nothing can be proven in medicine by statistics, it is apparent that Pasteur could have proceeded in no other way than he has done, in order to demonstrate the value of his treatment, and that the statistical method is the only one applicable to this demonstration, although we are to keep in mind all possibilities of error belonging to the method.

There are various careful collections of statistics which show that a conservative estimate of the average mortality of persons bitten by rabid animals is about 15 per cent. (Lablanc, Dujardin-Beaumetz, Horsley). The results of different statistics on this point vary widely, as is to be expected from the fact that they include generally in large but variable numbers bites from animals not proven to be rabid. On this point Pasteur's statistics have the merit of greater accuracy. It is logical to suppose that the statistics with large mortality include a greater proportion of bites from actually rabid animals than those with small mortality.

All agree that bites on the head and face by rabid animals furnish the highest mortality. This is given by Brouardel as 88 per cent. If we place it at 60 to 80 per cent., we are likely certainly not to exaggerate the mortality.

If now we contrast with these moderate estimates of the mortality following the bites of rabid animals, the results ob-

tained by Pasteur's method of treatment, there is left no room for doubt that this treatment has been proven to be efficacious, and has saved already hundreds of lives. I call attention especially to the convincing character of the results in persons bitten on the head and face by animals proven to be rabid.

The Pasteurian treatment, as is apparent from the preceding statistics, has a certain number of failures to record. It is not therefore unfailing, although if we compare its results with those obtained by methods of medical treatment in various diseases, it takes a very high rank, perhaps second only to vaccination in small-pox. The death from hydrophobia in two instances of persons over two years after treatment, casts a certain shadow upon the results, but can not invalidate the general conclusions as to the efficacy of the treatment.

It is most encouraging that the results of the treatment have improved with each successive year of its application. This is attributable to improvements in the methods, and is even more strikingly illustrated in the statistics of some others than in those of Pasteur, but I have preferred in this article to consider only the results obtained under Pasteur's immediate supervision. Essentially similar results, however, have been obtained in various places, chiefly in Russia, Italy and South America. The principal improvement in the method, as first applied by Pasteur, is in the elaboration of the so-called intensive method of preventive inoculation which is applicable to severe cases, especially to those bitten in the head or face and by wolves. In some anti-rabic institutes the intensive method has entirely superseded the simple method.

It is a sufficient answer to the assertion that has been made that Pasteur's intensive inoculations are dangerous, in that they may actually produce the disease, that the mortality from rabies is strikingly smaller after the application of the intensive method than after the simple treatment. There is, furthermore, a method of demonstrating experimentally that those who may die from rabies after preventive inoculations have not contracted the disease by means of the inoculations. These inoculations are made with the fixed virus, of which the period of incubation in rabbits after sub-dural injection is six or seven days; whereas those treated were bitten by animals affected with rabies of the street, the virus of which after sub-dural in-

oculation of rabbits has a period of incubation of fifteen to twenty days. As has been already mentioned, even if the period of incubation of the fixed virus be lengthened by dilution or attenuation of the virus, or if it be used to kill another animal as a dog, the virus as obtained from the brain or cord of the latter animal is still fixed virus, and will destroy rabbits with a period of incubation of six or seven days. Now, in all instances in which the brain or cord of a human being dying of rabies after the Pasteurian treatment has been used to inoculate rabbits, it has been found to contain virus with the period of incubation of rabies of the street, and not fixed virus, or in other words, not the kind of virus which was used for the preventive inoculation.

We are not to forget that the measures which are of first importance in preventing hydrophobia must be directed against the development and extension of the disease in dogs; for if canine rabies could be eradicated, there need be no fear of the disease, at least in this country and in eastern Europe. These measures consist in good dog laws, and their efficient application. A proper tax-rate upon dogs, their muzzling, and the destruction of stray and ownerless dogs, are the principal measures. It may be well also to enforce quarantine measures against dogs imported from countries where rabies is prevalent. In most parts of Germany these preventive measures are thoroughly enforced, and the result is an almost total disappearance of rabies; whereas in France similar measures are not carried out, and rabies is consequently alarming prevalent. I do not know of any data which enable us to determine the extent of prevalence of rabies in this country; but so far as can be judged by general impressions, it does not seem to be common with us. Its occurrence at all, however, is sufficient reason for the enforcement of those measures which have been found most efficient in its prevention.

